REMARKS

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections in view of the foregoing amendments and following remarks.

Claim 28 has been amended only to further limit it by incorporating the subject matter of claims 36 and 43 and further limiting the scope of the claimed active agent. Claim 58 has been amended only to limit it by incorporating the subject matter of claim 43 and further limiting the active agent. Claims 30, 34-36, and 43 have been canceled. No new matter has been added. Thus, Applicants submit that because all of the claimed subject matter has been previously examined, no new search is required, and the amendments should be entered.

Interview Summary

During the interview with the Examiner on December 17, 2008, the above amendments were discussed. Specifically, it was indicated that the proposed claims will be limited to a specific compound in claim 58 for the method claim and limited to group (f) in claim 28 and also limiting the claims to unilamellar liposomes having PC and DMPG in 70:30% ratio. The Examiner also suggested the following: 1) recite ranges of reduction of hemolysis; 2) compare with liposomes containing different amounts of PG. The Examiner also requested clarification regarding the experiment on page 28; whether PC used in formulations 2 and 4 are the same as in formulation 1. Since the

application is under final a continuation might be filed. The Examiner will determine the allowability after further search.

Claim Rejections- 35 U.S.C. § 112

Claims 28-49 and 53-56 and 58 were rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner asserts that although the specification is enabling for Na-(2,4,6-triisopropylphenyl sulfonyl)-3-amidino-(D,L)-phenylalanine-4-ethoxy carbonylpiperazide (WX-UK1) encapsulated in liposomes containing PC and PG in specific ratios and hemolysis as the side effect, the specification does not provide enablement for generic liposomes and multitudes of compounds fitting the generic derivatives of amidino and guanidine phenylalanine derivatives of the general formula. Without acceding to the propriety of the allegations, and in hopes of advancing prosecution, Applicants submit that independent claims 28 has been limited to a small genus comprising the compound Na-(2,4,6-triisopropylphenyl sulfonyl)-3-amidino-(D,L)-phenylalanine-4-ethoxy carbonylpiperazide encapsulated in unilamellar phospholipidic liposome containing PC and DMPG in a specific ratio and hemolysis as the reduced side effect. Further, claim 58 has been limited to a method of reducing unwanted hemolysis side effects and claim 28 has been limited to a small genus comprising the compound Na-(2,4,6-triisopropylphenyl sulfonyl)-3-amidino-(D,L)-phenylalanine-4-ethoxy carbonylpiperazide (WX-UK1), the L enantiomer thereof, a pharmaceutically suitable salt thereof, or a combination thereof. Applicants submit that the claims are now very specific and would enable those of

ordinary skill in the art to use the claimed invention. Thus, Applicants request that the rejection under §112 be withdrawn.

Claim Rejections- 35 U.S.C. § 103

Claims 28-49, 53-56 and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 or DE 10225876.7. Additionally, the Examiner cites the references Caster (5,776,486), Poiani (5,660,822), and Steck (4,186,183) for encapsulating active agents in a liposome.

With regard to Caster, the Examiner refers to a very unspecific statement,

> Liposomes are used as carriers for drugs. Liposomes can be made with different features which can enhance a drug's efficacy; reduce a drug's toxicity; and prolong the drug's therapeutic effect (col. 1, lines 33-36)

which does not contain any information as to composition, interaction with the active agent, or physiological properties of liposomes. While quite a few phospholipids are mentioned, there is no indication whatsoever of preferred phospholipids and/or combinations thereof. In Caster, the working examples are based on a mixture of 60% PC and 16.5%PE, soy-PC or pure cholesterol. Thus, Caster relates to specific drugs contained in liposomes. Caster further qualifies the above generalization in col. 30, lines 49-53:

> The in vitro stability of liposomes will generally depend on several parameters, such as phospholipid composition and purity, oxygen

susceptibility, compatibility between encapsulated drugs and liposomes, and aqueous medium conditions.

Thus, it is clear that the cited reference teaches that it is not obvious if liposomes will be successful. The present claims are limited to a specific drug (WX-UK1) and a specific unilamellar phospholipid comprising phosphatidylcholine and dimyristoylphosphatidyl glycerol in a ratio of about 70:30 by weight, and specific effective amount of Na-(2,4,6-triisopropylphenyl sulfonyl)-3-amidino-(D,L)-phenylalanine-4-ethoxy carbonylpiperazide (WX-UK1). Clearly, Caster does not teach or suggest the presently claimed liposomal formulation or methods. In combination with WO 00, Caster would not suggest the presently claimed specific formulation, amounts, and phospholipids types. Furthermore, the combination of Caster and WO 00 would not render obvious a method of reducing hemolysis side effect using the specific active agent which is effective as a urokinase inhibitor and capable of reducing hemolysis side effects are recited in claim 58.

With regard to Poiani, the Examiner refers to the disclosure of col. 11, lines 12-22 of Poiani directed to the use of liposomes to reduce drug toxicity. Applicants submit that Poiani describes the use of an antifibrotic agent, particularly cis-4-hydroxyl-L-proline (cHyp), which is operatively linked to a monomer or polymer. In Example 16, a liposome consisting of L-α-dipalmitoylphosphatidylcholine, cholesterol and stearylamine is described. Poiani teaches that encapsulation in the liposome was necessary for drug action. Injection of free cHyp was ineffective (see col. 30, lines 22-24). There is no

disclosure of the instantly claimed active ingredient, a specific unilamellar phospholipid comprising phosphatidylcholine and dimyristoylphosphatidyl glycerol in a ratio of about 70:30 by weight, specific effective amount of the active ingredient, or reducing hemolysis. Applicants submit that no combination of Poiani and WO 00 would suggest the presently claimed specific formulation, amounts, and phospholipids types. Furthermore, the combination of Poiani and WO 00 would not render obvious a method of reducing hemolysis side effect using the specific active agent which is effective as a urokinase inhibitor and capable of reducing hemolysis side effects as recited in claim 58.

With regard to Steck, the Examiner asserts that liposome encapsulated drugs would have decreased liability for producing toxic side effects (col. 2, lines 32-33). Steck relates to lipsome carriers for the active agents megluminantimonate and sodiumstiboglutamate. The disclosed phospholipids are lecithin, γ-dipalmitoyl-α-lecithin, sphingomyelin, phosphatidylserine, phsphatide acid, cholesterol, coprostanol, cholestanol and cholestanone. In the examples a ratio of 2:1.5 phospholipid to cholesterol are used (col. 6, lines 46-48). Further liposomal formulations in Table 2 all include cholesterol. Further, Steck experiments with various liposomal formulations to determine their effectiveness. Thus, it is not obvious from Steck that any liposome would be effective. Steck does not teach or suggest the presently claimed liposome formulation (unilamellar phospholipid comprising phosphatidylcholine and dimyristoylphosphatidyl glycerol in a ratio of about 70:30 by weight), the instantly claimed active ingredient, the specific effective amount of the active ingredient, or

reducing hemolysis. Thus, Applicants submit that the combination of WO 00 and Steck would not have rendered obvious the presently claimed formulations and methods. Furthermore, the combination of Steck and WO 00 would not render obvious a method of reducing hemolysis side effect using the specific active agent which is effective as a urokinase inhibitor and encapsulating the active agent in a specific phopholipidic liposome capable of reducing hemolysis side effects as recited in claim 58.

Claims 28-32, 41-48, 53-56 and 58 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 (English equivalent is US 2003/0013723) or DE10225876.7 by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck(4,186,183) by themselves or in combination, further in combination with WO 88/09168. The Examiner asserts that WO 88 discloses liposomal formulations containing doxorubicin for the treatment of tumors, wherein the liposomes contain lecithin, phosphatidylglycerol, cholesterol, and cryoprotectant. The Examiner asserts that it would have been obvious to use the liposomes of WO 88 in the generic teachings of WO 00. Applicants submit that the arguments above and the amendments to the claims overcome the obviousness rejections based on any combination of WO 00 and Caster, Poiani, and Steck. Further, with regard to the Examiner's allegations based on WO 88, Applicants submit that WO 88 teaches that low toxicity results from high integrity of the liposome encapsulating the drug, DXR, which is reported by a low percentage of free DXR (c.f. WO 88, page 24, lines 31-35). Applicants submit that the instant specification provides evidence from experiments that show that the specific liposomal composition (unilamellar phospholipid comprising phosphatidylcholine and

dimyristoylphosphatidyl glycerol in a ratio of about 70:30 by weight) claimed herein has high integrity for encapsulating WX-UK1 and results in a very low percentage of free WX-UK1 when compared with a control liposome (100% phosphatidylcholine)-(see Example 6). WO 88 does not teach or suggest the presently claimed liposomal components, the active ingredients claimed herein, the active amounts of the drugs claimed herein, or reducing hemolysis. No combination of WO 88 and WO 00 would render obvious all of the features of the presently claimed formulation. Thus, Applicants submit that the present claims are nonobvious and request that the rejections be withdrawn. Further, the subject matter of claims 36 and 43 are incorporated into claims 28 and 58. Thus, Applicants submit that because the subject matter of claim 36 was not rejected as being obvious in view of the references cited above, the rejections of claims 28 and 58 should be withdrawn. Claims 29, 31-32, 41, 42, 44-48, and 53-56, depending from claim 28 should be allowable for at least the reasons above.

Claims 34-43 and 49 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 (English equivalent is US 2003/0013723) or DE10225876.7 by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck(4,186,183) by themselves or in combination with Barenholz (U.S. 6,156,337). The Examiner asserts that Barenholz discloses using DMPC and DMPG without giving amounts on column 9, and that it is within the skill of those in the art to mix these two phospholipids in suitable appropriate amounts. Barenholz is directed to loading liposomes with biopolymeric substances, for example Factor VII, VIII, IX, X, XIII, fibrinogen, thrombin or prothrombin, which are all very large, complex

polypeptides. These active agents are substantially different than the instantly claimed agent. Further, the basis for selection of DMPC and DMPG apart from stability is uptake by macrophages (c.f. col. 9, lines 19-30). Applicants submit that one of skill in the art would not have, after reading the disclosure of Barenholz, been motivated to prepare the presently claimed formulation. First of all, Barenholz discloses liposomes consisting of DMPC and DMPG in a ratio of 9:1 (c.f. col. 11, line 59, col. 12, line 39) or DMPC:DMPG:cholesterol in a ratio of 9:1:7.5 (col. 10, lines 24-25). There is no disclosure in Barenholz of a liposome comprising phosphatidylcholine and dimyristoylphosphatidyl glycerol in a ratio of about 70:30 by weight, the active agent WX-UK1, the concentration of the active agent, or reducing hemolysis side effect. One of ordinary skill in the art would have to take quite a leap to combine a reference teaching a different combination of phospholipids (DMPC/DMPG), at a different ratio (9:1), with a different drug (polypeptides), where the liposomes was suitable for a different purpose (uptake of macrophages), and combine it with WO 00 to arrive at the presently claimed formulation and method. Applicants submit that based on the amendments and arguments above, no combination would have rendered obvious the presently claimed invention and request that the rejections be withdrawn.

Claims 28-49, 53-56, and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 (English equivalent is US 2003/0013723) or DE10225876.7 by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck(4,186,183) by themselves or in combination, further in combination with Ben-Hur (6,010,890) or Kurono (4,906,477). The Examiner maintains

that these references disclose that liposomes reduce hemolysis by the active agent and, combined with the above references, render the present claims obvious. First of all, Applicants submit, based on the above reasoning, no combination of the cited references teaches or suggests the presently claimed formulation. It is clear that the inventors have developed a liposome composition that avoids leaking (see Example 6), reduces unwanted side effects such as skin irritation, pain, and inflammation as demonstrated in Example 2, system toxicity as demonstrated in Example 3, as well as hemolysis as demonstrated in Example 5. Thus, the claimed formulation and method is not obvious and should be allowable for at least the reasons by themselves. However, to further bolster the points made above, Applicants submit that there is actually disclosure in Ben-Hur and Kurono that further supports the nonobviousness of the presently claimed formulation.

Ben-Hur relates to a method of reducing the level of infectious virus contained in red blood cells and is not related to a urokinase inhibitor drug. The composition of Ben-Hur is a phthalocyanine and more particularly Pc4 formulated in a liposome carrier. While Ben-Hur states in col. 6, lines 62-65 that "... formulation of Pc4 in liposomes resulted in less hemolysis, and ...", it is further stated in col. 7, lines 15-19 and Fig. 4 that "the results (Fig. 4) show great differences in the ability of equivirucidal doses to cause red blood cell damage, depending on the liposome composition." Further, in col. 7, lines 1-4, Ben-Hur discloses that "compositions containing PEG or cholesterol...also reflected in greatly enhanced hemolysis of red cells." Therefore, Ben-Hur provides evidence that some liposomes enhance hemolysis while others reduce hemolysis. The

present inventors have conducted experiments to find a very specific formulation which interacts well with the specifically claimed drug, encapsulates it with high integrity, and thereby reduces hemolysis. Ben-Hur does not teach or suggest the presently claimed liposome composition.

Kurono relates to an encapsulated Adriamycin from the group of anthracycline antibiotics, which differs from the presently claimed urokinase inhibitor. The aim of Kurono is to maximize the amount of the antibiotic encapsulated in the liposome to reduce cardiotoxicity and nephrotoxicity (col.2, lines 23-25). The liposome of Kurono consists of phophatidylcholine, cholesterol, and steroidal sulfate (col. 2, lines 50-53). Steroidal sulfate is chosen because the drugs of Kurono have a high affinity for binding to steroidal sulfate by electrostatic force (see abstract). The examples of Kurono only disclose a liposomes consisting of phophatidylcholine, cholesterol, and steroidal sulfate in ratios of 6:1:3 and 6:3:1 (see col. 6, line 56). There is no data from any other liposome encapsulating the antibiotics. There is no suggestion in Kurono that <u>any</u> liposome would reduce hemolysis. Most importantly, the liposome formulation of Kurono is specifically formulated to encapsulate Adriamycin. There is no mention of a unilamellar phospholipids liposome, said liposome consisting of PC and DMPG, said PC and DMPG being in a weight ratio of 70:30, encapsulating WX-UK1, or the amounts of WX-UK1 to be used.

Applicants submit that no combination of the cited art renders obvious the presently claimed formulation or method because no combination mentions the

presently claimed liposome or puts forth any teaching that would motivate one of skill in the art to make the presently claimed formulation or practice the presently claimed method after reading WO 00.

Applicants submit that the cited references are improperly combined and that, nevertheless, it would not have been obvious for one of ordinary skill in the art to know the proper amounts of the active ingredient, the specific type of liposome effective for encapsulating the active ingredient, and the specific components of the liposome useful for producing the formulation. Applicants submit that the prior art cited herein disclose many different drugs, many different liposomes, and many different disease targets. It is clearly not obvious to combine all of these references and arrive at a single specific formulation or method as are presently claimed.

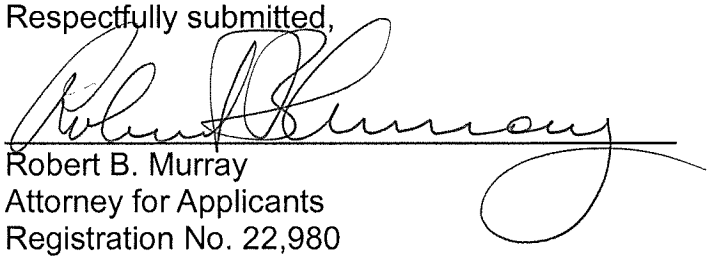
In response to the rejections above, given that claims 28 and 58 should be allowable over the cited art, it follows that claims 29, 31-33, 37-42, 44-49, and 53-56, all depending on claim 28, should also be allowable.

Conclusions

In view of the above amendments and remarks hereto, Applicants believe that all of the Examiner's rejections set forth in the October 21, 2008 Office Action have been fully overcome and that the present claims fully satisfy the patent statutes. Applicants, therefore, believe that the application is in condition for allowance. The Director is authorized to charge any fees or overpayment to Deposit Account No. 02-2135.

The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

By 

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